220. New Sesquiterpenoids from Clary Sage Oil (*Salvia sclarea* L.)[1])

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Summary

Six sesquiterpenoids, (2*R*,5*E*)-2,12-epoxycaryophyll-5-ene (**1**), (2*R*,5*E*)-caryophyll-5-en-12-al (**2**), (2*S*,5*E*)-caryophyll-5-en-12-al (**3**), isospathulenol (**4**), (1*R*,5*R*)-1,5-epoxysalvial-4(14)-ene (**5**), and salvial-4(14)-en-1-one (**6**) have been identified for the first time in clary sage oil (*Salvia sclarea* L.). The structures and absolute configurations of **1**–**6** are corroborated by partial syntheses and their organoleptic properties are discussed.

The compounds **5**, **6** and mintsulfide (**14**) possess the rare C-skeleton **C**, for which the semisystematic name 'salvialane' is proposed. The sesquiterpenoids **1**–**5** are new.

1. Introduction

Clary sage oil is obtained by steam distillation of the flowers and foliage of *Salvia sclarea* L. *(Labiatae)* and is widely used in perfumery and flavors [1]. The chemical composition of this important perfumery raw material of various geographical origins has been investigated by several workers [2–7]. To our knowledge, no analytical work using the GC-MS technique has been reported. Up to now, *ca.* 70 compounds have been identified which represent over 96% of the total weight. The main components are linalyl acetate (*ca.* 67%), linalool (*ca.* 16%) and several mono- and sesquiterpene hydrocarbons (*ca.* 13%). Mixing these main constituents in the correct ratio, however, does not reproduce the odor of sage which is characteristically sweet and herbaceous with undertones of ambergris and tobacco.

Aiming at a synthetic reconstitution, we have analyzed commercial clary sage oil by the usual techniques of isolation (fractional distillation, chemical separation, CC and GC) and identification (NMR, GC-MS and direct comparison with authentic samples). More than 250 compounds have been identified, mainly by GC-MS. Among these are six new sesquiterpenoid constituents which are the subject of this paper.

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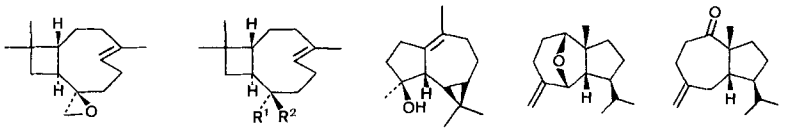
[1]) Presented, in part, at the IXth International Congress of Essential Oils, Singapore, March 13–17, 1983, and at the Meeting of the Swiss Chemical Society in Berne, October 14, 1983.

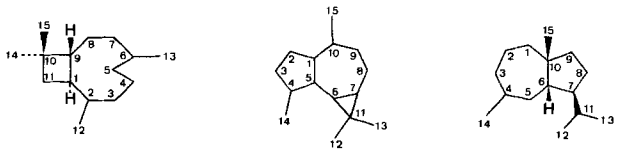
In the course of analysis of a medium-boiling fraction (b.p. 40–70°/0.1 Torr, 3.5% of the total oil) in which a characteristic part of the clary sage odor was concentrated, we isolated, in addition to known compounds[2]), six new constituents **1**–**6**.



1 **2** R^1 = H, R^2 = CHO **3** R^1 = CHO, R^2 = H **4** **5** **6**

The chemical constitutions of these compounds were deduced by high-field ^{1}H- and ^{13}C-NMR spectroscopy (making extensive use of decoupling techniques and lanthanide shift reagents) in combination with IR and MS. The relative and absolute configurations were established by partial syntheses.

The compounds possess three different C-skeletons: the very common caryophyllane (**A**)[3]) and aromadendrane (**B**), and the exceedingly rare salvialane (**C**)[4]) skeleton.



A **B** **C**

2. Structure Elucidations and Partial Syntheses. – *Caryophyllanes* **1**–**3**. The structural analogy of these three compounds was demonstrated by the partial conversion of compound **1** to a mixture (*ca.* 1:1) of **2** and **3** upon injection into the heated port (240°) of a gas chromatograph. The mass spectra (M^+ at m/z 220) and the ^{1}H-NMR spectra (24 protons) indicated the empirical formula $C_{15}H_{24}O$ for all three compounds. The caryophyllane skeleton was suggested by the ^{1}H-NMR spectra (the signals for the three CH_3-groups and the olefinic proton in **1**–**3** parallel those of caryophyllene, see *Exper.*

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[2]) This fraction contained the following main components: geranyl acetate, 3,6-diacetoxy-2,6-dimethyl-1,7-octadiene, (−)-caryophyllene [4] [6], (−)-germacrene-D [6], (−)-caryophyllene oxide [8] (both diastereomers) and (+)-spathulenol [9]. Minor amounts of bicyclogermacrene [10], isocaryophyllene [11], isocaryophyllene oxide [8] [12] (both diastereomers), (−)-(*E*)-12-norcaryophyll-5-en-2-one (**12**) [13], (2*R*,5*R*,6*R*)-2,12:5,6-diepoxycaryophyllane (**7**) [14], dihydro-α-agarofuran [15] and (−)-mintsulfide (**14**) [16] [17] were also identified by comparing the spectral data (^{1}H-NMR, MS) and retention times with those of authentic samples.

[3]) Among the various numbering systems for caryophyllane, (see for example [13] [14] [18] [19]), we prefer the numbering proposed by *Kaiser & Lamparsky* [13] which follows the IUPAC recommendations.

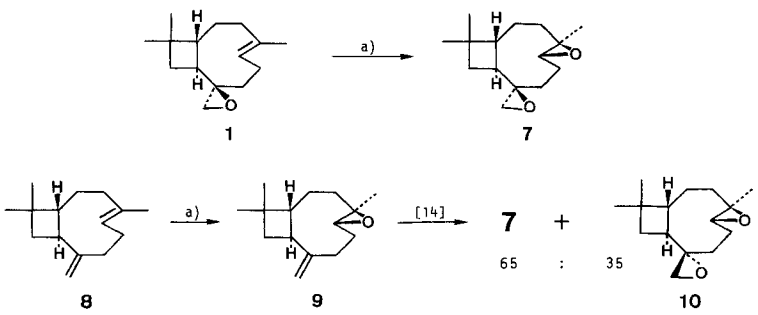
[4]) We propose the semisystematic name 'salvialane' for skeleton **C** which implies the absolute configuration and numbering shown (using the fixed numbering of germacrane). To our knowledge, the only natural compounds isolated so far with this C-skeleton are periplanone A [20] and (−)-mintsulfide (**14**) [16]. The latter is also present in clary sage oil (see *Footnote 2*) and many other essential oils [17].

Part) and by the MS (**1**–**3** show a typical fragment ion at *m/z* 164 ($M^+ - 56$) resulting from the characteristic loss of isobutene from the molecular ion [13]).

The IR spectrum of **1** showed no carbonyl absorption and the ^{1}H-NMR spectrum indicated a disubstituted epoxide (*AB*-system with $\delta_A = 2.53$, $\delta_B = 2.60$, $J_{AB} = 5$ Hz). Compounds **2** and **3** were easily recognized as aldehydes (IR absorptions at 2830, 2730 and 1720 cm^{-1} and ^{1}H-NMR signals at 9.69 for **2** and 9.35 ppm for **3**). These data led us to putatively propose the structures **1**–**3**, without, however, any information about the configuration of these compounds.

The structure and absolute configuration of the epoxide **1** was confirmed by conversion into the known diepoxide **7** [14] by peracid oxidation *(Scheme 1)*, a reaction which was highly stereoselective. The same diepoxide **7** was obtained as the major product from the epoxidation of (−)-caryophyllene oxide (**9**) together with the diastereoisomer **10** (ratio 65:35) [14]. Because the specific rotations of the diepoxide **7** obtained from either monoepoxide were the same, the new epoxide **1** has the relative and absolute configuration shown.

Scheme 1



a) AcOOH, NaOHc, CH_2Cl_2.

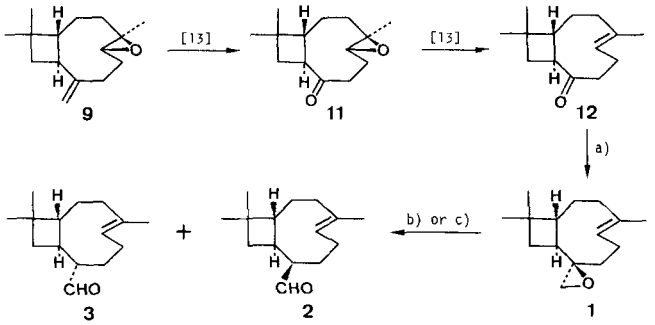
Distinction between aldehydes **2** and **3** from their spectral data was not possible. Knowing, however, that the configuration of the oxirane ring in **1** is β and that **2** is the kinetic product of the epoxide → aldehyde rearrangement (**2** epimerizes under equilibrating conditions to a 1:1 mixture of **2** and **3**), we may safely assign the β-configuration of the formyl group to **2**. It is well known that this rearrangement proceeds stereospecifically with in-plane 1,2-H-shift (see, *e.g.*, [21] [22]).

To verify the structures of the compounds **1**–**3** and to submit them for olfactive evaluation, their syntheses from (−)-caryophyllene oxide (**9**) were effected *(Scheme 2)*.

The reaction of **12** [13] with dimethylsulfonium methylide gave only one epoxide, which was identical (IR, ^{1}H-NMR, MS) with natural **1**. This highly stereoselective reaction parallels the observation by *Kaiser & Lamparsky* [13] that methylmagnesium iodide also adds to **12** exclusively from the α-face.

Rearrangement of epoxide **1** using $MgBr_2$ in ether gave an epimeric mixture of the two aldehydes **2** and **3** (ratio *ca.* 10:1) which was equilibrated in the presence of BF_3-

Scheme 2



a) $(CH_3)_3S^{\oplus}I^{\ominus}$, NaH, DMSO/15–20°/15 h. b) $MgBr_2$, Et_2O/25°/1 h. c) $BF_3 \cdot Et_2O$, Et_2O/20°/1 h.

etherate to give a 1:1 mixture. The aldehydes **2** (peak 1) and **3** (peak 2), isolated by prep. GC (*Silicone GE XE 60*, 190°), were found to be identical (^{1}H-NMR, MS, retention time) with the natural compounds.

More direct routes for the synthesis of **1**–**3** from caryophyllene (**8**) were unsuccessful. For example, methods such as hydroboration [23], hydroalumination and epoxidation with peroxybenzimidic acid [24] resulted in reactions involving the strained endocyclic double bond of **8**.

It is surprising that the simple oxygenated derivatives **1**–**3** of the widely occurring sesquiterpene caryophyllene (**8**) have neither been synthesized nor reported to occur in nature. On the other hand, oxygenated derivatives of **8**, involving the more strained endocyclic double bond at C(5) (or both double bonds), are common (*e.g.* caryophyllene oxide [13] [25], kobusone [13] [26], *etc.*).

Whereas the epoxide **1** has a weak woody odor, the mixture of the aldehydes **2** and **3** displays an unexpected musky-woody note and is of potential interest to perfumery.

Isospathulenol (**4**). The mass spectrum of this new compound *(Fig. 1)* was strikingly similar to that of (+)-spathulenol (**13**) [9] [27] [28] (the major sesquiterpene alcohol of clary sage oil, *cf. Footnote 2*).

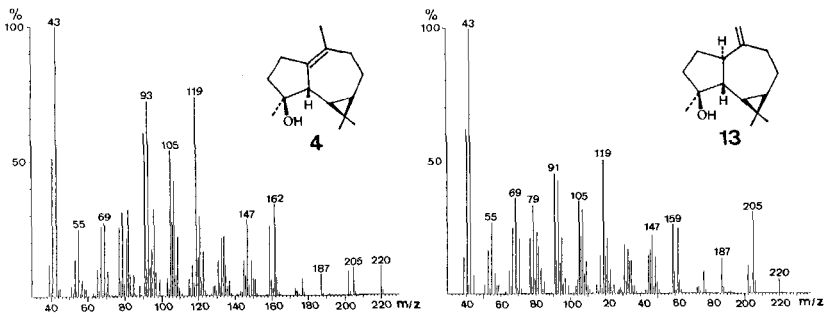
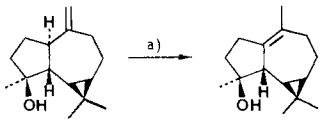


Fig. 1. *Mass spectra* (70 eV) *of isospathulenol* (**4**) *and spathulenol* (**13**)

The ^{1}H- and ^{13}C-NMR spectra of **4** (see *Exper. Part*) indicated the presence of a tetrasubstituted double bond (with one substituent being a CH_3-group), three further CH_3-groups at quaternary C-atoms and a cyclopropane ring bearing two protons. These data suggested **4** to be an isomer of **13** in which the exocyclic double bond has been rearranged.

Treatment of (+)-spathulenol (**13**, isolated from clary sage oil) with TsOH gave a complex mixture from which **4** ($[\alpha]_D = +105.5°$ ($c = 1.1$, $CHCl_3$)) was isolated in crystalline form (m.p. 69–70.5°). This compound was identical (MS, ^{1}H-NMR, retention time) with the natural product **4**, thus proving the chemical constitution and relative configuration of **4**[5]).

Scheme 3



13 **4**

a) TsOH, Et_2O/reflux/10 h

The odor of (+)-spathulenol (**13**) has been described as earthy-aromatic [27]. (+)-Isospathulenol (**4**) has a similar odor.

1,5-Epoxysalvial-4(14)-ene (**5**). The mass spectrum *(Fig. 3)* (M^+ at m/z 220) and the ^{1}H-NMR spectrum *(Fig. 2)* (24 protons) indicated the empirical formula $C_{15}H_{24}O$, and the IR spectrum showed neither carbonyl- nor OH-absorption bands. The ^{1}H-NMR spectrum (360 MHz) revealed the presence of an exocyclic CH_2-group [4.79 and 4.71 (2 br. *s*, 2 H)], two methine groups bearing an O-atom [4.44 (*d*, $J = 8$, 1 H) and 3.76 (br. *d*, $J = 4.5$, 1 H)], a CH_3-group on a quaternary C-atom [1.25 (*s*, 3 H)] and an isopropyl group [0.85 and 0.83 (2 *d*, $J = 6.5$, 6 H), *ca.* 1.32 (*m*, 1 H)]. Irradiation experiments (in the absence and presence of the lanthanide shift reagent Eu(fod)$_3$) allowed each proton to be assigned and the chemical constitution to be unambiguously determined. The relative configuration of the chiral centers C(1), C(5), C(6) and C(10) followed from the ^{1}H-NMR spectrum and for geometric reasons: C(1) and C(5), as are C(6) and C(10) are interdependent because they are the bridgehead atoms of an 8-oxabicyclo[3.2.1]octane and a *cis*-3-oxabicyclo[3.3.0]octane moiety, respectively; (two *trans*-fused five-membered rings would be highly strained). The *endo*-configuration of the cyclopentane ring was indicated by the coupling constant between the two adjacent bridgehead protons ($J(5,6) = 8$ Hz). The relative configuration of the fifth chiral center at C(7) was not obvious, but structure **5** with the β-isopropyl group fits better with the spectral data than its C(7)-epimer and is supported by biogenetic considerations (formation from (−)-germacrene-D).

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[5]) Although the sample of **4**, isolated from clary sage oil, was too small for measurement of the optical rotation, its absolute configuration corresponds almost certainly to that of (+)-spathulenol (**13**). This was shown to be the case for (**4**) ($[\alpha]_D = +99°$ ($c = 0.6$, $CHCl_3$)) isolated from petitgrain oil (*Citrus aurantium*, subsp. *amara*), where it occurs in substantial amounts, together with **13** ($[\alpha]_D = +6.6°$ ($c = 0.5$, $CHCl_3$)).

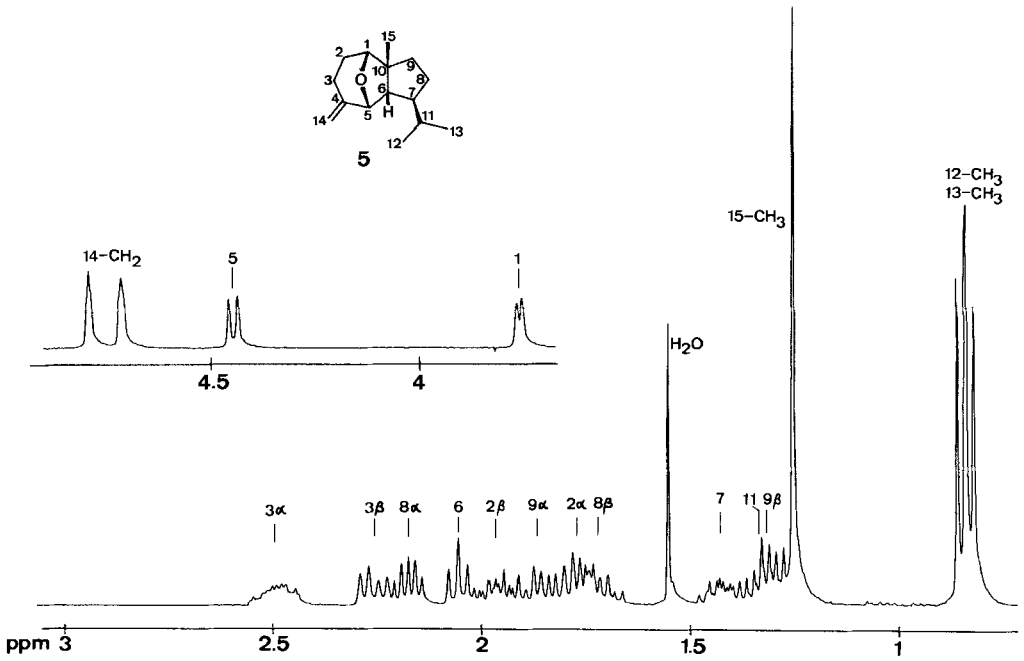


Fig. 2. *^{1}H-NMR spectrum* (360 MHz, $CDCl_3$) *of 1,5-epoxysalvial-4(14)-ene* (**5**)

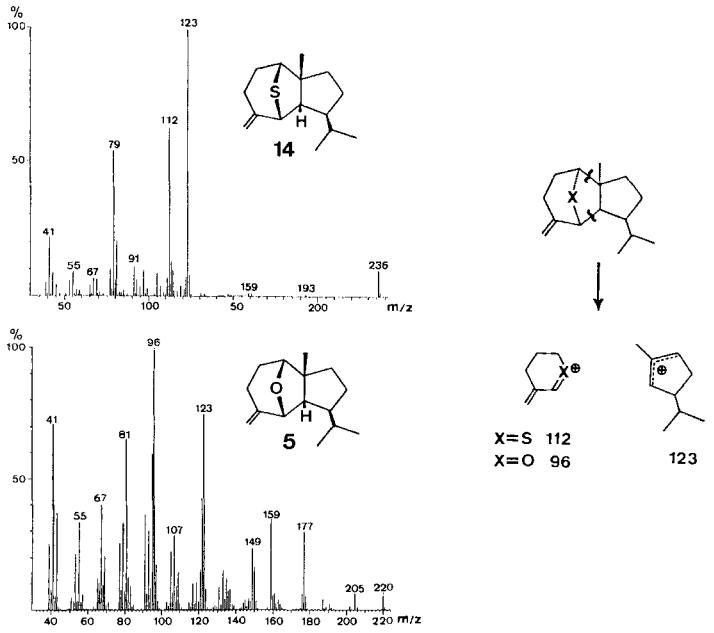


Fig. 3. *Mass spectra* (70 eV) *of mintsulfide* (**14**) *and 1,5-epoxysalvial-4(14)-ene* (**5**)

Ether **5** is the O-analog of mintsulfide (**14**), a S-containing sesquiterpene recently isolated from peppermint oil [16] and other essential oils [17]. The structure of (−)-mintsulfide (**14**) has been determined by X-ray crystallography, and the compound has also been synthesized by the photoinduced reaction of (−)-germacrene-D with elemental sulfur [16] [17], thus proving its absolute configuration. As both compounds (**14** and germacrene-D) co-occur in many essential oils (*e.g.* also in clary sage oil, see *Footnote 2*), they are presumably related biogenetically [17].

The MS, ^{1}H- and ^{13}C-NMR-spectra of ether **5** (see *Exper. Part*) parallel those of mintsulfide (**14**) [16] [17]. In particular, the MS of both compounds *(Fig. 3)* show abundant fragment ions due to the cleavage of the central ring: *m/z* 123 and 112 for **14** and 123 and 96 for **5**.

The structure and absolute configuration of **5** were confirmed by synthesis (see next *Chapter* and *Exper. Part*).

Salvial-4(14)-en-1-one (**6**). The mass spectrum of **6** *(Fig. 4)* suggested a close relation between this compound and its isomer **5**. The only striking difference concerns the fragment ion at *m/z* 96, which is the base peak of **5** *(Fig. 3)* but of a negligible intensity in **6**. As this ion is due to the cleavage of the central ring in **5**, this ring is probably absent in **6**. This was supported by the ^{1}H-NMR spectrum *(Fig. 5)*, which, although not revealing protons at O-substituted C-atoms, still indicated the presence of an exocyclic CH_2-group [4.76 and 4.71 (2 br. *s*, 2 H)], a CH_3-group at a quaternary C-atom [1.19 (*s*, 3 H)] and an isopropyl group [0.98 and 0.88 (2 *d*, J = 6.5, 6 H), *ca.* 1.58 (*m*, 1 H)]. That the O-atom was part of a non-conjugated ketone function, was indicated by the IR spectrum (strong absorption at 1700 cm^{-1}) and the ^{13}C-NMR spectrum (*s* at 215.7 ppm). With this information and by analogy with compound **5**, structure **6** for this ketone seemed likely. This compound has been obtained previously by the biomimetic cyclization of germacrene-D 1,10-epoxide [20], but without definitive proof of its structure. Our ^{1}H-NMR spectrum of **6** is in agreement with the reported data.

To gain chemical evidence for the structure of **6**, we removed the carbonyl function by *Wolff-Kishner* reduction and the double bond by catalytic hydrogenation *(Scheme 4)*. This gave a mixture of the two epimeric salvialanes (**17a/b**). The same two hydrocarbons **17a/b** were obtained from the reductive desulfuration of (−)-mintsulfide (**14**) with *Raney*-Ni, followed by catalytic hydrogenation of the mixture of olefins **16**. This chemical correlation established the C-skeleton and relative configuration of **6**, whereas the position of the carbonyl group followed unambiguously from the ^{1}H-NMR spectrum.

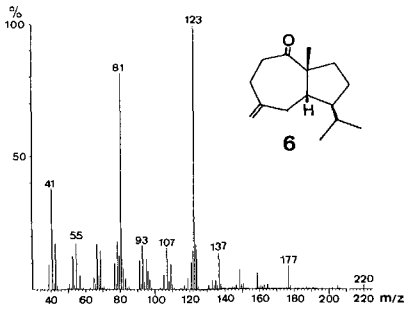


Fig. 4. *Mass spectrum of* **6** (70 eV)

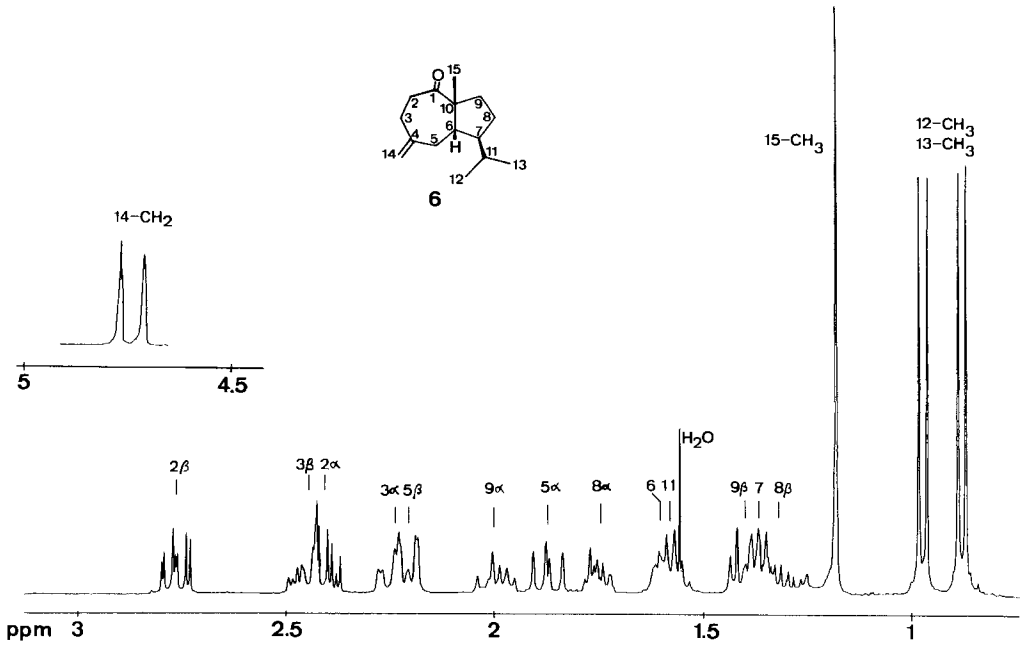
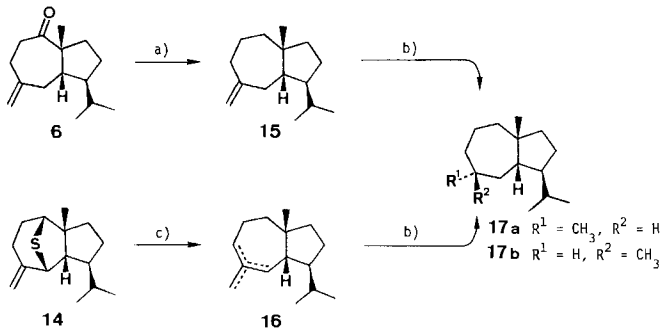


Fig. 5. *^{1}H-NMR spectrum* ($CDCl_3$, 360 MHz) *of* **6**

Scheme 4



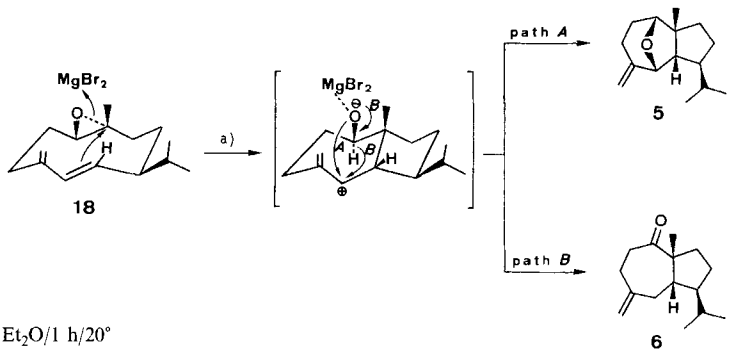
a) N_2H_4, KOH, diethylene glycol/140–190°/2 h. b) H_2, Pd/C (10%), EtOH/15 h. c) *Raney*-Ni, MeOH/reflux/24 h.

The structures and absolute configurations of both compounds, **5** and **6**, were confirmed by synthesis *(Scheme 5)*.

Germacrene-D 1,10-epoxide (**18**) [29], whose absolute configuration is known, was cyclized in the presence of $MgBr_2$ in Et_2O to give a complex mixture (*cf.* the biomimetic reactions of **18** [20] [29] [30]) from which the compounds **5** and **6**[6]) could be isolated in

[6]) The formation of ketone **6** by treatment of **18** with basic alumina has been reported [20].

Scheme 5



a) $MgBr_2$, Et_2O/1 h/20°

low yield. Both compounds were identical ($[\alpha]_D$, ^{1}H-NMR, MS and retention time) with the natural products, thus proving their absolute configuration.

It is interesting to compare the odor of ether **5** with that of the S-analog mintsulfide (**14**). The former has a relatively weak spicy-floral note with a camphoraceous undertone. It smells stronger than **14** whose odor was reported as heavy, woody and earthy [17]. We find the odor of **14** rather uncharacteristic and very weak. The ketone **6** shows a full, pleasant woody note reminiscent of ambergris and vetiver with a spicy-floral undertone. It is typical of the odor of clary sage oil.

We thank Professor *A. Eschenmoser* and Dr. *A. F. Thomas* for helpful discussions and *Dr. G. Ohloff* for his continuous interest in this work.

Experimental Part

(with the valuable collaboration of Mr. *J. C. Froidevaux*)

1. General Remarks. See [31]. Optical rotations are for $CHCl_3$-solutions.

2. Isolation from Clary Sage Oil. Fractional distillation of commercial clary sage oil (3000 g, presumably of French origin) through a *Vigreux* column gave a fraction (107 g, 3.5%; b.p. 40–70°/0.1 Torr) still having a typical sage odor and containing mainly sesquiterpenoids. This fraction was chromatographed on neutral alumina[7]) (1000 g, *Woelm*, activity grade II) using PE (b.p. 50–70°)/Et_2O to give the following fractions: A) 63 g (eluted with 2 l of PE, mainly hydrocarbons); B) 13.9 g (eluted with 1 l of PE/Et_2O 8:2), containing geranyl acetate and several oxygenated sesquiterpenes; C) 7.2 g (eluted with 1 l of PE/Et_2O 1:1) containing mainly caryophyllene oxide (**9**) (not further investigated); D) 9.7 g (eluted with 1 l of Et_2O) containing geraniol and spathulenol (**13**) as main constituents.

Fraction A, containing caryophyllene (t_R = 0.464)[8]), germacrene-D (t_R = 0.608)[8]) and bicyclogermacrene (t_R = 0.646)[8]) was fractionally distilled on a packed column (20 cm). The fraction with b.p. 70–71°/0.1 Torr (0.4% of the total oil) contained *ca.* 90% of germacrene-D, *ca.* 10% of bicyclogermacrene and traces of other sesquiterpenes. It was directly used for the preparation of germacrene-D 1,10-epoxide. A sample of pure *germacrene-D* was isolated by prep. GC (*Carbowax* first, then silicone). $[\alpha]_D^{20} = -280°$ (c = 0.4, $CHCl_3$) ([6]: $[\alpha]_D = -188°$ (EtOH), [32]: $[\alpha]_D^{23} = -240°$, [33]: $[\alpha]_D = -305°$ (MeOH)). The spectra (IR, ^{1}H-NMR and MS) were the same as shown in [6] and [34].

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[7]) Using silica gel instead of alumina resulted in the complete decomposition of germacrene-D, *cf.* [32].

[8]) Relative retention times (t_R) of identified natural product (t_R for caryophyllene oxide = 1.00) refer to GC using a glass capillary column (50 m, I.D. 0.32 mm) coated with *UCON 5100*, oven temp. 80–180°, 2°/min.

Fraction B was distilled (bulb-to-bulb, 100–120°/0.5 Torr) and the distillate dissolved in a few ml of hexane. After seeding with a crystal of caryophyllene oxide, the solution was left for 4 days at −10° to give 1.1 g of almost pure caryophyllene oxide (**9**). The mother-liquor was distilled using a *Fischer* column *(Mikro)* to remove the solvent and the main part of geranyl acetate (2.6 g, b.p. 40–45°/0.1 Torr). The residue was again dissolved in hexane to give a second crop (1.2 g) of **9** after 4 days at −10°. Repeated chromatography of the mother-liquor (6.6 g) on a 100-fold amount of silica gel (*Merck* 0.063–0.2 mm) with PE/Et_2O 98:2→80:20 allowed the following sesquiterpenoid compounds to be isolated and characterized (in order of elution on silica gel).

Dihydro-α-agarofuran (t_R = 0.681)[8]). Identical (^{1}H-NMR, MS) with authentic material, *cf.* [15].

(2 R,5 E)-2,12-Epoxycaryophyll-5-ene (**1**) (t_R = 0.996)[8]). $[\alpha]_D$ = +40° (*c* = 3.4). Identical (IR, ^{1}H- and ^{13}C-NMR, MS, t_R) with the synthetic material.

(2 R,5 R,6 R)-2,12:5,6-Diepoxycaryophyllane (**7**) (t_R = 1.602)[8]). M.p. 60–62°, $[\alpha]_D^{20}$ = −61.2° (*c* = 1) ([14]: m.p. 76–77°, $[\alpha]_D$ = −69° (*c* = 1.71)). Identical (IR, ^{1}H-NMR, MS, t_R and $[\alpha]_D$) with samples obtained by epoxidation of **1** or **9**.

(2 R,5 E)-Caryophyll-5-en-12-al (**2**) (t_R = 1.109)[8]). Oil (*ca.* 80% pure), $[\alpha]_D$ = +6.7° (*c* = 1.1). Identical ($[\alpha]_D$, IR, ^{1}H-NMR, MS, t_R) with the synthetic material.

(2 S,5 E)-Caryophyll-5-en-12-al (**3**) (t_R = 1.171[8]). Oil (97% pure) $[\alpha]_D$ = −21.9° (*c* = 1.1). Identical with the synthetic material.

Salvial-4(14)-en-1-one (**6**) (t_R = 1.037)[8]). M.p. 31–32°, $[\alpha]_D^{20}$ = +59.7° (*c* = 1.6). Identical ($[\alpha]_D$, IR, ^{1}H-NMR , MS, t_R) with the synthetic sample obtained from (−)-germacrene-D 1,10-epoxide (**18**), *cf.* [20].

(1 R,5 R)-1,5-Epoxysalvial-4(14)-ene (**5**) (t_R = 0.908)[8]). M.p. 61–62°, $[\alpha]_D^{20}$ = +40.5° (*c* = 1.0). Identical ($[\alpha]_D$, IR, ^{1}H-NMR, MS, t_R) with the synthetic sample obtained from **18**.

(E)-12-Norcaryophyll-5-en-2-one (**12**) (t_R = 0.952)[8]). M.p. 26–27°, $[\alpha]_D^{20}$ = − 71.5° (*c* = 1.4) ([13]: m.p. 32.5°, $[\alpha]_D^{20}$ = −78.7° (*c* = 1.28)). Purity *ca.* 90% (by ^{1}H-NMR). Identical with a synthetic sample prepared according to [13]. IR (liq.): 1700*s*, 1460*m*, 1380*m*, 1175*m*, 1130*m*, 1105*m*. ^{1}H-NMR (360 MHz): 0.98 (*s*, 3 H); 1.02 (*s*, 3 H); 1.76 (br. *s*, 3 H); 2.85 (*q*, *J* = 8.5, 1 H); 5.25 (br. *t*, *J* = 7.5, 1 H). ^{13}C-NMR (90.5 MHz): 15.9 (*q*); 21.9 (*t*); 23.1 (*q*); 28.9 (*t*); 29.3 (*q*); 33.4 (*s*); 35.8 (*t*); 39.9 (*t*); 40.7 (*t*); 51.9 (*d*); 52.6 (*d*); 122.7 (*d*); 138.0 (*s*); 216.0 (*s*). MS: 206 (5, M^+), 41 (100), 55 (91), 93 (62), 108 (57), 67 (56), 81 (54), 107 (47), 79 (47), 95 (43), 69 (34), 39 (31), 41 (30), and further characteristic fragments at 121 (21), 150 (19), 135 (17), 122 (16).

Caryophyllene Oxide (**9**) (t_R = 1.000)[8]). M.p. 60.5–61°, $[\alpha]_D^{20}$ = −70.4° (*c* = 1.32) ([8]: m.p. 63.5–64°, $[\alpha]_D^{20}$ = −79.4° (*c* = 2.32)). Identical with an authentic sample.

Fraction D was subjected to prep. GC (*Carbowax*, 220°). The following compounds were isolated: *Spathulenol* (**13**) (t_R = 1.201)[8]). Oil, $[\alpha]_D^{20}$ = +5.4 (*c* = 1.12) ([27]: $[\alpha]_D^{22}$ = +5.7° (*c* = 1.97)). IR: identical with spectrum in [27]. ^{1}H-NMR (360 MHz): 0.47 (*dd*, *J* = 11 and 10, 1 H); 0.71 (*ddd*, *J* = 11, 10 and 6, 1 H); 1.04 (*s*, 3 H); 1.06 (*s*, 3 H); 1.29 (*s*, 3 H); 2.42 (*dd*, *J* = 13 and 6, I H); 4.67 and 4.69 (2 br. *s*, 2 H); in agreement with [27] and [28]. ^{13}C-NMR: see [35]. MS: see *Fig. 1*.

Isospathulenol (**4**) (t_R = 1.371)[8]). M.p. 69–70.5°, $[\alpha]_D$: see *Footnote 5*. Identical (m.p., ^{1}H-NMR, MS and t_R) with the sample obtained from **13**.

3. Chemical Correlations. – *3.1. Epoxidation of Epoxide* **1**. *Diepoxide* **7** *(Scheme 1)*. To a solution of epoxide **1** (isolated from clary sage oil, 63 mg, 0.286 mmol) in CH_2Cl_2 (1 ml) were added at r.t. NaOAc (40 mg) and 40% peracetic acid (57 µl, 0.44 mmol). The mixture was stirred at r.t. for 5 h, diluted with Et_2O and washed with 10% aq. Na_2CO_3-solution and brine. After evaporation of the solvent, the residue was distilled (bulb-to-bulb, 100–130° (oven)/0.1 Torr) to give 57 mg (84%) of diepoxide **7** (purity *ca.* 90%). A pure sample was obtained by prep. GC (*Carbowax*, 230°). $[\alpha]_D$ = −67° (*c* = 0.9). The diepoxide thus obtained was identical ($[\alpha]_D$, ^{1}H-NMR, MS, t_R) with crystalline **7** obtained from **9** according to [14]. M.p. 76–77°, $[\alpha]_D$ = −69° (*c* = 1.71). IR ($CHCl_3$): 3020*m*, 1470*m*, 1400*m*, 1385*w*, 1080*w*, 880*w*. ^{1}H-NMR (360 MHz): 0.93 (*s*, 3 H); 0.95 (*s*, 3 H); 1.04 (*td*, *J* = 13 and 4, 1 H); 1.20–1.58 (several overlapping *m*, total 8 H); 1.27 (*s*, 3 H); 1.67 (*td*, *J* = 4 and 15, 1 H); 1.78 (*t*, *J* = 10, 1 H); 2.03–2.22 (several overlapping *m*, 4 H); 2.57 (*d*, *J* = 5, 1 H); 2.68 (*d*, *J* = 5, 1 H); 3.09 (*dd*, *J* = 10.5 and 4, 1 H); *cf.* [14]. MS: 236 (< 1, M^+), 43 (100), 41 (61), 55 (51), 108 (41), 93 (37), 79 (36), 69 (31), 95 (28), 67 (27), 71 (25), 81 (24), 91 (22).

3.2. Reduction of Ketone **6**. – *Mixture of Salvialanes* (**17a/b**) *(Scheme 4)*. A mixture of ketone **6** (50 mg, isolated from clary sage oil), KOH (50 mg), hydrazine hydrate (0.15 ml) and diethylene glycol (1.5 ml) was heated to 140° (1 h) in a simple distillation apparatus. The water formed was allowed to distill and the temperature was risen to 190°. After 3 h at 190°, the mixture was cooled, diluted with H_2O and extracted with Et_2O. The crude extract (34 mg), consisting mainly of hydrocarbon **15** (by GC-MS analysis), was hydrogenated over Pd/C (10%) in EtOH to give a mixture (19 mg after distillation) of two epimeric hydrocarbons **17a/b** (peak 1/

peak 2 ratio *ca.* 1:4 on a *UCON* glass capillary column, assignment tentative according to GC-MS analysis).

17a (Peak 1): MS: 208 (8, M^+), 95 (100), 81 (86), 41 (82), 55 (81), 109 (75), 69 (64), 67 (45), 82 (44), 83 (43), 123 (38), 193 (33), 43 (30), and further characteristic fragments at 96 (28), 124 (25), 165 (22), 137 (18).

17b (Peak 2): MS: 208 (5, M^+), 95 (100), 81 (87), 55 (74), 109 (72), 41 (72), 69 (53), 67 (42), 123 (41), 83 (41), 82 (40), 165 (34), 124 (30), and further characteristic fragments at 96 (24), 193 (21), 137 (17).

3.3. Desulfuration of (−)-Mintsulfide (**14**). A solution of **14** (159 mg, synthesized from (−)-germacrene-D following [17]) in MeOH (3 ml) was heated at reflux with a large excess of *Raney*-Ni for 24 h. The catalyst was removed by filtration and the filtrate evaporated. The oily residue (120 mg), consisting of a complex mixture of saturated and unsaturated hydrocarbons **16** (by GC-MS), was hydrogenated in EtOH in the presence of Pd/C (10%) to give a mixture (109 mg, ratio *ca.* 1:4) of the same two hydrocarbons **17a/b** (by GC-MS) as obtained above.

4. Synthesis of Individual Constituents. – *4.1. (2* R,*5* E*)-2,12-Epoxycaryophyll-5-ene* (**1**) *(Scheme 2).* NaH-dispersion (80% in oil, 8.1 g, 0.27 mol) was placed in a 1-l three-necked flask with a magnetic stirrer and twice washed with PE to remove the mineral oil. DMSO (300 ml) was added and the mixture was stirred at r.t. for 15 min. Trimethylsulfonium iodide (61.4 g, 0.3 mol) was added, followed after 5 min by the addition at 10–15° of a solution of **12** [13] (30.9 g, 0.15 mol) in DMSO (50 ml). Stirring was continued overnight at r.t. and the mixture was poured into a large excess of ice/H_2O. The mixture was extracted with PE, the extract washed neutral (brine), dried (Na_2SO_4), and the solvent evaporated. Distillation of the crude product (32 g) through a *Vigreux* column gave 28.8 g (87%) of epoxide **1**, b.p. 71–72°/0.1 Torr in *ca.* 90% purity. The product was identical with natural **1** (spectral data and t_R) and contained *ca.* 10% of starting ketone **12** and traces of aldehydes **2** and **3**. None of the epimeric epoxide was detected by capillary GC or ^{1}H-NMR. Epoxide **1** was difficult to purify, because it was quite unstable in air and partly rearranged to **2** and **3** when injected in the heated port of a GC. IR (liq.) 3050*w*, 1680*w*, 1470*sh*, 1460*m*, 1395*m*, 1380*m*, 1300*m*, 1010*w*, 890*m*. ^{1}H-NMR (360 MHz): 0.92 (*s*, 3 H); 0.94 (*s*, 3 H); 1.26–1.56 (several *m*, 4 H); 1.63 (br. *s*, 3 H); 1.68–2.10 (several *m*, 7 H); 2.20 (*m*, 1 H); 2.56 (*AB*-system, $J_{AB} = 5$, $\delta_A = 2.53$, $\delta_B = 2.60$, 2 H); 5.50 (*m*, 1 H). MS: 220 (< 1, M^+), 41 (100), 55 (58), 79 (52), 69 (50), 91 (47), 67 (45), 81 (43), 93 (40), 119 (35), 134 (29), 107 (29), 43 (29), and further characteristic fragments at 149 (10), 164 (7), 176 (4).

4.2. (2 R,*5* E*)- and (2* S,*5* E*)-Caryophyll-5-en-12-al* (**2** and **3**, respectively). A solution of **1** (17.6 g, 80 mmol, containing *ca.* 10% of **12**) in dry Et_2O (50 ml) was added at r.t. during 30 min to a solution of $MgBr_2$ (8.7 mmol) in Et_2O (prepared from 300 mg of Mg and 0.75 ml of 1,2-dibromoethane in 10 ml of Et_2O). Stirring was continued at r.t. for 30 min and the mixture was poured into ice/H_2O and extracted with Et_2O. Evaporation of the solvent and distillation of the crude product (18.0 g) gave 13.2 g (75%) of a mixture of aldehydes **2** and **3** (ratio 5:1), containing *ca.* 10% of **12** and *ca.* 10% of the corresponding (5*Z*)-aldehydes. When a solution of this mixture (600 mg) in Et_2O (5 ml) was stirred with BF_3-etherate (0.1 ml) at r.t. for 1 h, the ratio of **2**/**3** changed from 5:1 to *ca.* 1:1 (not changing further on prolonged stirring). Aldehydes **2** and **3** were isolated from this mixture by prep. GC (silicone, 190°). The compounds (especially **2**) were difficult to purify due to their tendency to isomerize. Both compounds were identical (spectral data and t_R) with the natural aldehydes.

(2 R,*5* E*)-Isomer* **2** (shorter t_R). Oil, $[\alpha]_D^{20} = +6.7°$ (*c* = 1.05, purity *ca.* 80%). IR ($CHCl_3$): 3020*w*, 2830*w*, 2730*w*, 1720*s*, 1675*w*. ^{1}H-NMR (360 MHz): 0.99 (*s*, 6 H); 1.64 (br. *s*, 3 H); 5.26 (*m*, 1 H); 9.69 (br. *s*, 1 H), and other unresolved signals. MS: 220 (2, M^+), 135 (100), 41 (98), 79 (67), 93 (66), 67 (55), 69 (53), 81 (52), 107 (50), 55 (49), 95 (41), 91 (36), 164 (27), and further characteristic fragments at 133 (25), 121 (24), 136 (15), 149 (14), 187 (6), 205 (4), 177 (4).

(2 S,*5* E*)-Isomer* **3**. Oil, $[\alpha]_D^{20} = -21.9°$ (*c* = 1.14, purity *ca.* 97%). IR ($CHCl_3$): same bands as for **2**. ^{1}H-NMR (360 MHz): 0.95 (*s*, 3 H); 0.96 (*s*, 3 H); 1.64 (br. *s*, 3 H); 2.43 (*m*, 1 H); 5.45 (*m*, 1 H); 9.35 (*d*, *J* = 4, 1 H), and other unresolved signals. MS: 220 (2, M^+), 135 (100), 41 (46), 79 (33), 93 (32), 69 (27), 67 (27), 81 (24), 55 (24), 107 (22), 95 (17), 91 (15), 136 (13), and further characteristic fragments at 121 (7), 164 (6), 163 (5), 191 (4).

4.3. (+)-Isospathulenol(**4**) *from (+)-*(**13**) *(Scheme 3).* A solution of **13** ($[\alpha]_D^{20} = +5.4°$ (*c* = 1.1), 120 mg, isolated from clary sage oil) in Et_2O (2 ml) was heated to reflux for 10 h under Ar in the presence of TsOH (10 mg). The mixture was washed with 10% aq.Na_2CO_3-solution, the solvent evaporated and the residue (120 mg) chromatographed on silica gel (10 g) with PE/Et_2O 75:25. After a fraction of unidentified hydrocarbons (*ca.* 90 mg), **13** (8 mg) and isospathulenol (**4**) (20 mg, 18%) were obtained. The latter was purified by prep. GC (*Carbowax*, 230°) and recrystallized from acetonitrile. M.p. 69–70.5°, $[\alpha]_D = +105.5°$ (*c* = 1.1). Identical (^{1}H-NMR, MS, t_R) with natural **4**. IR ($CHCl_3$): 3600*m*, 3425 br., 1460*s*, 1385*s*, 1100*s*, 925*m*. ^{1}H-NMR (360 MHz): 0.58 (*m*, 2 H); 1.01 (*s*, 3 H); 1.12 (*s*, 3 H); 1.25 (*s*, 1 H, disappears after shaking with D_2O); 1.29 (*s*,

3 H); 1.57 (br. *s*, 3 H), and other unresolved signals. ^{13}C-NMR (90.5 MHz): 16.1 (*q*); 18.9 (*s*); 21.7 (*q*); 22.2 (*t*); 24.4 (*q*); 25.4 (*d*); 28.5 (*q*); 29.5 (*t*); 32.2 (*d*); 36.5 (*t*); 38.7 (*t*); 49.2 (*d*); 81.5 (*s*); 126.5 (*s*); 137.3 (*s*). MS: see *Fig. 1*.

4.4. 1,5-Epoxysalvial-4(14)-ene (**5**) *and Salvial-4(14)-en-1-one* (**6**) *from Germacrene-D 1,10-epoxide* (**18**) *(Scheme 5). – Germacrene-D 1,10-epoxide* (**18**)[9]). Because the standard procedure for the epoxidation of germacrene-D (**15**) with *m*-chloroperbenzoic acid [36] was unsatisfactory in our hands, the following procedure was used. To a stirred mixture of NaOAc (3.28 g, 40 mmol) and peracetic acid (40%, 4 ml, 30.8 mmol) in CH_2Cl_2 (40 ml) was added at $-60°$ (−)-germacrene-D (**15**) (*ca.* 90% purity, isolation described above, 4.08 g, 20 mmol). The mixture was allowed to reach r.t. After stirring at r.t. for 30 min, the mixture was washed with 10% aq. Na_2CO_3-solution and H_2O, dried ($MgSO_4$) and the solvent evaporated. Distillation of the residue (bulb-to-bulb, 80–90°/0.05 Torr) gave 4.0 g (91%) of crude epoxide **18** (purity *ca.* 70%), containing unreacted **15** (*ca.* 15%), **13** (*ca.* 10%, probably arising from bicyclogermacrene by epoxidation, followed by transannular cyclization), **6** (*ca.* 5%), and traces of other compounds. We were not able to purify the crude epoxide **18** by CC (aluminia or silica gel) or GC as it was quite unstable and decomposed under basic (*cf.* [20] [30]) and acidic (*cf.* [29]) conditions. Capillary GC (50 m, *UCON*) showed that only one stereoisomer **18**[9]) was formed. ^{1}H-NMR (90 MHz): 0.86 (*d*, *J* = 6, 3 H); 0.91 (*d*, *J* = 6, 3 H); 1.29 (*s*, 3 H); 2.58 (*dd*, *J* = 10 and 4, 1 H); 4.89 (br. *s*, 2 H); 5.47 (*dd*, *J* = 16 and 9, 1 H); 6.04 (*d*, *J* = 16, 1 H), *cf.* [36]. MS (of pure **18** by GC-MS): 220 (6, M^+), 43 (100), 80 (75), 79 (52), 123 (50), 41 (49), 81 (48), 93 (43), 91 (43), 69 (35), 94 (30), 55 (30), 107 (26), and further characteristic fragments at 119 (24), 177 (21), 159 (20), 149 (11).

To a solution of crude **18** (70%, 2.86 g, 13 mmol) in dry Et_2O (30 ml) was added under N_2 at $-60°$ a 2M etheral solution of $MgBr_2$ (1 ml, 2 mmol, prepared from 1.22 g of Mg (51 mmol) and 7.5 g (40 mmol) of 1,2-dibromoethane in 20 ml of dry Et_2O). The mixture was allowed to reach r.t., dry THF (10 ml) was added, and stirring was continued at r.t. for 90 min. The mixture was poured into ice/H_2O containing some NH_4Cl and extracted with Et_2O. After evaporation of the solvent, the residue (3.0 g) was distilled (bulb-to-bulb, 80–120° (oven)/0.05 Torr) to give 2.4 g of a complex mixture, containing **5**, **6**, **13** and alcohol **19**[10]) as main constituents. Chromatography of this mixture through silica gel (400 g) with PE/Et_2O 9:1→1:1 gave a fraction (282 mg) containing mainly **5** (peak 1, *ca.* 40%) and **6** (peak 2, *ca.* 60%), which were separated by prep. GC *(Carbowax)* and found to be identical with the natural compounds.

5 (Peak 1): oil, $[\alpha]_D^{20} = +40.2°$ ($c = 0.77$). IR ($CHCl_3$): 3060*w*, 1650*w*, 910*m*. ^{1}H-NMR (360 MHz). *Fig. 2*. ^{13}C-NMR (90.5 MHz): 21.7 (*q*); 21.9 (*q*); 25.4 (*t*); 27.9 (*t*); 31.7 (*q*); 32.9 (*t*); 35.0 (*d*); 36.7 (*t*); 47.8 (*d*); 55.0 (*s*); 63.5 (*d*); 82.5 (*d*); 84.7 (*d*); 110.8 (*t*); 145.0 (*s*). MS: *Fig. 3*.

6 (Peak 2): oil, $[\alpha]_D^{20} = +61.4°$ ($c = 0.96$). IR (liq.): 3080*w*, 1700*s*, 1650*w*, 1465*m*, 1085*m*, 905*m*. ^{1}H-NMR (360 MHz): *Fig. 5*. ^{13}C-NMR (90.5 MHz): 19.7 (*q*); 22.1 (*q*); 25.4 (*q*); 27.2 (*t*); 32.8 (*d*); 33.6 (*t*); 34.8 (*t*); 39.3 (*t*); 42.7 (*t*); 52.1 (*d*); 54.8 (*d*); 59.3 (*s*); 111.9 (*t*); 148.5 (*s*); 215.7 (*s*). MS: *Fig. 4*.

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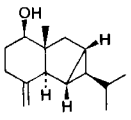
[9]) For the assignment of the configuration of **18**, see [29].

[10]) *6α,8α-Cycloselin-4(14)-en-1β-ol* has been characterized as a major product (11% yield) from the reaction of **18** with basic alumina [30]. Our compound showed the same ^{1}H-NMR spectrum.



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